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·Review·

Phosphoinositide pathway and the signal transduction network in neural development

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Abstract: The development of the nervous system is under the strict control of a number of signal transduction pathways, often interconnected. Among them, the phosphoinositide (PI) pathway and the related phospholipase C (PI-PLC) family of enzymes have been attracting much attention. Besides their well-known role in the regulation of intracellular calcium levels, PI-PLC enzymes interact with a number of molecules belonging to further signal transduction pathways, contributing to a specific and complex network in the developing nervous system. In this review, the connections of PI signalling with further transduction pathways acting during neural development are discussed, with special regard to the role of the PI-PLC family of enzymes.

Keywords: phospholipase C; CNS development; calcium release

1 Introduction

The development of the nervous system is a complex, tightly-regulated process involving a number of signal transduction pathways. The phosphoinositide (PI) signaling system regulates the levels of intracellular Ca^{2+} by means of converting enzymes, such as the phosphoinositide-specific phospholipase C (PI-PLC) family. Ca^{2+} is a ubiquitous second messenger involved in various cell activities, including proliferation and survival, differentiation, adhesion and cytoskeletal dynamics[1].

During the development of the nervous system, Ca^{2+} acts in further important events such as dendrite morphogenesis, axon guidance[2] and neurite morphogenesis[3]. Dendritic spine dynamics depends on the actin cytoskeleton and related regulatory proteins, some of which are sensitive to changes of Ca^{2+} concentration[4]. Developing neurites are guided to their targets by environmental factors to form the precise wiring of distinct neural circuits. In response to guidance cues, the growth cones at the tips of the neurites extend or retract[5]. The movements are probably driven by Ca^{2+} influx, which also regulates cytoskeletal dynamics, and the positioning of vesicles in synaptic areas[4].

The PI signal transduction pathway contributes to the regulation of Ca^{2+} levels in nervous tissue[3,6]. Besides, PI-PLC enzymes interact with a number of molecules. In this review, the involvement of PI-PLC enzymes in the development of the nervous system and their crosstalk with further signalling systems are analyzed.

2 PI signal transduction system

The PI signal transduction pathway is involved in a variety of cell functions such as hormone secretion, neu-

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rotransmitter signal transduction, cell growth, membrane trafficking, ion channel activity, cytoskeletal regulation, cell cycle control, and apoptosis, as well as cell and tissue polarity[4,7].

The role of PI in signal transduction was first described in 1953[8]. Signals involved in processes such as differentiation, proliferation, and apoptosis induce changes in inositol metabolism. *Vice versa*, inositol metabolism is involved in the cascade of sequential events composing these complex processes[9,10]. A combination of compartmentalized and temporal changes in molecules belonging to the PI system, such as phosphatidyl inositol (4,5) bisphosphate (PIP2) or phosphatidyl inositol (3,4,5) trisphosphate (PIP3), elicits different cellular responses, including regulation of gene expression, DNA replication, and chromatin degradation.

PIP2 directly regulates a number of cell functions, including cytoskeletal reorganization, cytokinesis, membrane dynamics, nuclear events and channel activity[11]. Therefore, strict regulation of PIP2 levels by means of converting enzymes, such as PI-PLC, is essential for homeostasis[9].

3 PI-PLC family of enzymes

3.1 Functions The PI-PLC family of enzymes plays a central role in PI signalling by regulating the spatiotemporal balance of PI metabolism. Once activated by a wide array of stimuli, PI-PLC cleaves PIP2 into inositol trisphosphate (IP3) and diacylglycerol (DAG) in less than a second, both being crucial molecules in signal transduction[8].

IP3, a small water-soluble molecule, rapidly diffuses to the cytoplasm, where it releases Ca^{2+} from the endoplasmic reticulum (ER) by binding to IP3-gated Ca^{2+}-release channels located in the ER membrane[9]. The initial increase induced by IP3 propagates as a wave through the cytoplasm, often followed by a series of Ca^{2+} spikes.

DAG remains bound to the membrane and may be cleaved to release arachidonic acid, which either acts as a messenger in the inflammatory cascade, or is used in the synthesis of eicosanoids[12]. DAG may also activate the serine/threonine Ca^{2+}-dependent protein kinase C (PKC) family of enzymes. The Ca^{2+} increase moves PKC from the cytoplasm to the cytoplasmic face of the plasma membrane[13]. Once activated, PKC enzymes phosphorylate specific serine or threonine residues of target proteins[4,11,14].

3.2 Structure Thirteen mammalian PI-PLC isoforms have been identified, divided into six sub-families on the basis of amino-acid sequence, domain structure and mechanism of recruitment: β (1–4), γ (1,2), δ (1,3,4), ε (1), ζ (1) and η (1,2)[4,15-18].

The PI-PLC family covers a broad spectrum of interactions that contribute to membrane recruitment, including binding to PI, interaction with small GTPases from the Ras and Rho families or heterotrimeric G protein subunits, and recognition of specific sites in tyrosine kinase receptors[4,19]. The interactions depend on the specific structure of each subfamily. Isoforms within sub-families share sequence similarity, and a common domain organisation and general regulatory mechanism.

The PI-PLC subfamilies share a conserved core architecture containing an N-terminal pleckstrin homology (PH) domain followed by a series of elongation factor (EF)-hand motifs, a complex catalytic domain, and a C-terminal protein kinase C conserved region 2 (C2) domain[11,14]. The PH domain (110 amino-acids) binds mainly the PI and regulatory proteins[13]. The catalytic domain is formed by historically designated X and Y domains; the former (65 amino-acids) binds Ca^{2+}, and the latter (115 amino-acids) primarily binds the substrate. Both X and Y are composed of alternating α helices and β strands. The X and Y domains comprise the two halves of a catalytic triose phosphate isomerase (TIM) barrel flanked on the N-terminal side by the EF-hand domains and by the C2 domain at the C terminus. The TIM barrel is a distorted eight-strand (βα)8 barrel, present in a number of proteins. However, the active site topology of the PI-PLC enzymes is considered to be unique. The N-terminal half (X) is more conserved and contains the catalytic residues. The C-terminal half (Y) is crucial for recognizing the substrate. A rigid catalytic structure is formed, due to the complex network of hydrogen bonds and electrostatic interactions that stabilize the

side-chain positioning[11]. The catalytic TIM barrel domain, incorporating regions of high sequence similarity, is the most conserved domain, both structurally and functionally. The X/Y linker connects the two halves and is highly variable in length and sequence in all PI-PLC enzymes. Interestingly, the catalytic core of most mammalian PI-PLC enzymes is elaborated with unique domains underlying the evolution of unique modes of regulation.

The other domains have well-conserved general folds, but their ligand binding properties may differ. Besides the general common structure, differences in the domains contribute to specific regulatory mechanisms, which characterize the subfamilies[4,11]. For instance, PI-PLC ζ lacks the PH domain[4], while the PH domain from PI-PLC δ1 binds PIP2 with high affinity and might be flexibly positioned relative to the other three domains. Moreover, the central C2 domain interacts with both EF-hands and the catalytic TIM barrel[11]. In PI-PLC β2, the PH domain is packed tightly between the EF-hands and the TIM barrel, forming a compact and globular core[11] and mediates protein-protein interactions by binding the GTP-bound form of Rac and Cdc42[11]. The PH domain mediates the interaction with PIP3 required for the translocation and activation of PI-PLC γ1, depending on phosphatidylinositol 3-kinase. In the PI-PLC γ subfamily, the PH domain directly interacts with transient receptor potential cation channels (TRPCs).

The structure of the C-terminal extension from PI-PLC β forms a fold composed of three long coiled-coil helices[11]. The C-terminal extension of PI-PLC ε contains two ubiquitin-like folds[11], one of which, the RA2 domain, binds Ras GTPases owing to overall positive charge and specific residues involved in Ras-binding.

PI-PLC ε also contains a N-terminal cell-division control 25 guanine-nucleotide exchange factor domain, predicted to be structurally similar to son of sevenless, conferring the upstream small GTPase activator function[11].

In the PI-PLC γ subfamily, a highly-structured region is inserted (PLCγ-specific array; γSA) between the X and Y domains[11]. The γSA includes a second, 'split' PH domain. Probably, the two parts of the 'split' PH domain form a stable, single domain with a loop incorporating Src Homology domains[11].

3.3 Tissue distribution The distribution of PI-PLC enzymes is strictly tissue-specific. Due to the differences in structure and tissue distribution, each isoform probably bears a unique function in the modulation of responses.

PI-PLC isoforms have been detected in many tissues, preferentially in hematopoietic cell lines (PI-PLC β2 and γ2)[20] and in the nervous system (PI-PLC β1 and β4)[21-27]. Moreover, PI-PLC β1 is predominantly expressed in telencephalic principal neurons and cerebellar interneurons, and is closely associated with related signalling molecules in somatodendritic neuronal elements[28]. The dysregulation of PI-PLC β1 or β4 is suggested to be one mechanism that links neural and pancreatic dysfunction, not only in insomnia but also in the disorders accompanied by circadian rhythm disruption and metabolic syndrome[23].

PI-PLC δ1 is widely expressed in many tissues, especially in cultured cells[29]. PI-PLC δ3 has been identified in various histotypes, although at low concentrations[30]. PI-PLC δ4 is expressed in the brain and in regenerating tissues[4,31,32]. PI-PLC γ1 is expressed in keratinocytes and fetal cartilage, mainly in the cytoplasm[33-36]. PI-PLC ε occurs in many tissues[37,38]. PI-PLC ζ has been identified exclusively in spermatids[39]. PI-PLC η isoforms are highly expressed in neuron-enriched brain regions[40], although both enzymes have been detected in human umbilical vein endothelial cells[41].

However, the potentialities of PI-PLC are not highlighted. Intriguingly, differential expression of PI-PLC isoforms has been detected in normal with respect to pathological tissues, mainly tumours[42].

3.4 Distribution and role of PI-PLC enzymes in the nervous system PI-PLC isoforms play specific roles, based on their tissue-specific expression and involvement in diseases affecting the nervous system.

PI-PLC β1, highly expressed in the cerebral cortex and hippocampus[43,44], is activated by G-protein-coupled receptors that signal through $G_{q/11}$. PI-PLC β1 mediates activity-dependent cortical development and synaptic plasticity[45,46]. *Plcb1*-knockout mice develop epilepsy, minor abnormalities in the hippocampus[47], and specific behav-

ioral deficits in location recognition, probably due to the excessive neurogenesis and aberrant migration of adult-born neurons[48]. PI-PLC β1 is also required for activity-dependent regulation of synapse and dendritic spine morphology in developing barrel cortex[46].

PI-PLC β1 has been reported to act in human diseases affecting the nervous system. It is the molecular convergence point of several neurotransmitter pathways implicated in schizophrenia[47,48]. Kurian *et al.* have recently described an association of loss-of-function mutation in the PI-PLC β1 gene (PLCB1, OMIM *607120) with early-onset epileptic encephalopathy[49]. We also identified deletion of PLCB1 in four out of 15 orbitofrontal cortex biopsies from patients with schizophrenia[50].

PI-PLC β2 is used as a differentiation marker to evidentiate the development of taste buds, the sensory end organs for taste[51].

A PI-PLC β3 isoform specific to human cone photoreceptor neurons has been described[52]. Remarkably, the human gene which encodes PI-PLC β3 (PLCB3; OMIM *600230) maps to a genomic region associated with neurodegenerative diseases, such as Bardet-Biedl syndrome (OMIM #209900) and Best's vitelliform dystrophy (OMIM #153700).

PI-PLC β4 is highly expressed in cerebellar Purkinje cells beginning at late embryonic stages[53,54]. *Plcb4*-knockout mice present with cerebellar ataxia[47] and minor developmental abnormalities[55]. PI-PLC β4 is also used as an antigenic marker of a subset of unipolar brush cells, glutamatergic interneurons of the cerebellar granular layer[56].

PI-PLC γ1 is abundantly expressed by radial glia during fetal brain development. Its expression is inversely correlated with glial fibrillary acidic protein expression from the embryonic stage to adulthood[57]. Moreover, it is proposed that Shc/PLC γ-mediated control of neuronal migration plays an important role in the regulation of neocortex formation by TrkB[58,59].

PI-PLC ε is strictly associated with neuronal lineage differentiation[60]. It is abundantly expressed around embryonic day 10.5 (E10.5), specifically in the outermost layer of the neural tube. Later (E12), it occurs mainly in the marginal zone of brain, spinal cord, retina and olfactory epithelium. Its expression persists in terminally differentiated neurons, lacking regional specificity. In cultured neural stem cells (NSCs), the expression of PI-PLC ε coincides with the loss of nestin expression, induction of microtubule-associated protein 2 (MAP2) expression, and the appearance of neuronal morphology. The activity of PI-PLC ε, regulated by association with Ras and Rap, might play a role in intracellular signalling from receptors for fibroblast growth factor (FGF) and various neurotrophic factors involved in neural development[61]. As a matter of fact, members of the FGF family play critical roles during neural development from induction to terminal differentiation[62]. In PC12 pheochromocytoma cells, FGF and nerve growth factor (NGF), leading to the induction of neuronal differentiation, are required for activation of the Ras–Raf–MAPK pathway[63]. Rap and Ras have also been reported to oppositely control the synaptic plasticity of hippocampal neurons by regulating the trafficking of AMPA-sensitive glutamate receptors into excitatory synapses[64].

Recently, PLCH2 (OMIM *612836)[40], which encodes PI-PLC η2, was suggested to be involved both in syndromic (1p36 deletion syndrome, OMIM #607872) and isolated mental retardation[65] and in the pathogenesis of neuroblastoma[41].

4 PI-PLC enzymes in neural progenitor cells

Neural crest cells (NCCs) exhibit spontaneous Ca^{2+} transients[66]. Depleting the Ca^{2+} stores of the ER reduces the number of active cells and Ca^{2+} spiking frequency. The PI signal transduction system seems to be involved in this event. In fact, blockade of IP3 receptor (IP3R)-dependent Ca^{2+} release abolishes Ca^{2+} transient activity. Studies demonstrated that the primary co-activators of the IP3R are Ca^{2+} and IP3, one of the signalling molecules derived from PIP2 hydrolysis *via* PI-PLC[4]. NCCs displaying Ca^{2+} transients may generate neurons while blockade of the Ca^{2+} transient activity prevents the generation. Thus, spontaneous Ca^{2+} transient activity, probably regulated by PI-PLC enzymes, is required for neuronal differentiation of cultured NCCs[67].

The development of the mammalian nervous system is based on a balance between self-renewal and differentiation of NSCs. NSCs are present in developing and adult brain from early embryonic stages to senescence in specific regions such as the subventricular zone, hippocampus and olfactory bulb in the rodent[68]. Wnt signals are involved in multiple developmental processes including neurogenesis[69]. The Wnt pathway diverges into at least four branches. One is represented by the Wnt/Ca^{2+} pathway, which involves activation of PI-PLC and PKC. PI-PLC and PKC inhibitors block the increase of MAP2-positive cells with Wnt-5a, suggesting a major role in the differentiation of progenitor cells[70]. In NSCs, FGF induces prominent Erk1/2 and PI-PLC γ1 activation. The Erk1/2 pathway mediates both the proliferation and anti-neuronal differentiation effects of FGF-2. PI-PLC γ1 maintains adult NSC characteristics and the developmental potential for neuronal and oligodendroglial differentiation[71]. Coordination of these two pathways ensures that adult NSC self-renewal is under the stringent control of growth factor (GF) signalling networking the PI signalling.

5 Pathways related to PI-PLC activity

Recent evidence indicates that the PI signal transduction pathway and PI-PLC enzymes are connected with different hierarchy of control to a number of pathways involved in neural development, neurogenesis and the maintainance of synaptic plasticity.

5.1 CREB/MAPK CREB/MAPK, important transcriptional factors strongly dependent on Ca^{2+} transient frequency, belong to the signalling pathway of GFs in astrocytes[72]. Acute μ and κ opioids activate the ERK/MAPK phosphorylation cascade. By this crosstalk, opioids may impact neural development and plasticity. The μ agonist DAMGO induces a transient stimulation of ERK phosphorylation. The κ agonist U69,593 engenders sustained ERK activation. U69,593 and DAMGO stimulate ERK phosphorylation using different secondary messengers and PKC isoforms upstream of the GF pathway[73]. DAMGO activation of PKC ε and/or ERK is insensitive to selective inhibitors of Ca^{2+} mobilization, and is blocked by PI-PLC inhibition. This suggests that DAMGO activates PKC ε in a PI-PLC-dependent manner[73].

5.2 Adhesion molecules A number of membrane-associated and soluble proteins direct axonal outgrowth toward their targets *via* promoting or inhibiting effects[74,75], including the cell adhesion molecules (CAMs) of the Ig, cadherin, and integrin superfamilies[76]. During development, thalamocortical axons reside primarily in neocortical layer IV. In rat thalamic explants, axons form branches specifically in the target layer of fixed cortical slices, regardless of the orientation of the ingrowth[77]. Branch formation is probably regulated by local cues, independently of those governing axonal termination[78]. Cellular interactions mediated by CAMs might contribute to axonal branching. Polysialic acid, the sugar moiety attached to the neural cell adhesion molecule (NCAM), may regulate axon fasciculation in motor pathways by inhibiting branching in inappropriate layers[79]. NCAM plays a pivotal role in the development of the nervous system, promoting neuronal differentiation *via* homophilic as well as heterophilic interactions. NCAM-induced intracellular signalling depends on cytoplasmic Ca^{2+} regulation[80]. The homophilic binding site of NCAM (P2) increases Ca^{2+} levels in hippocampal neurons. This effect depends on two signalling pathways, one associated with the activation of fibroblast growth factor receptor and PI-PLC γ. NCAM-induced neurite outgrowth seems to depend on the activation of p59*fyn*, focal adhesion kinase, PI-PLC γ, PKC and the Ras/MAPK pathway[81].

5.3 Neurin-1 Neurin-1, otherwise termed PI anchor protein, is an axonal growth-related molecule anchored to the surface membrane, mainly associated with fiber-containing regions of the developing embryonic mouse brain. The anchorage of neurin-1 to the plasma membrane is strictly associated with the presence of PI and, therefore, to PI metabolism and PI-PLC activity[82].

5.4 Neurotrimin (Ntm) The expression pattern of Ntm suggests a role in the development of thalamocortical and pontocerebellar projections[83]. Ntm promotes dorsal root ganglion neuronal outgrowth after PI-PLC treatment, suggesting that its effects on outgrowth are mediated by

heterophilic interactions. PI-PLC treatment removes Ntm from the surface of neurons and abolishes the binding. However, PI-PLC treatment does not affect the ability to promote neurite outgrowth[84].

5.5 PACAP Pituitary adenylate cyclase-activating polypeptide (PACAP) is a pleiotropic neuropeptide belonging to the secretin/glucagon/vasoactive intestinal peptide family. PACAP and its receptor type 1 (PAC1) system regulate neurogenesis and gliogenesis, and prevent delayed ischemic neuronal death in the hippocampus[85]. PAC1 is expressed in neuroepithelial cells from early developmental stages and during development. The PACAP/PAC1 system regulates the differentiation of neural progenitor cells through the Gs-mediated and cAMP-dependent signalling pathway. Ectopic expression in cortical neuroblasts transforms the antimitotic effect of PACAP into a promitogenic signal, requiring PI-PLC pathway function, as indicated by the blockade induced by the PI-PLC antagonist U-73122[86].

5.6 Muscarinic receptors Adenylate cyclase and PI-PLC signalling systems are also coupled to muscarinic-cholinergic receptors (mAChRs) in the human fetal brain. Carbachol treatment of brain slices, in the presence of Li^+, results in the accumulation of PI, with rapid increases of IP3 and DAG. The cholinergic stimulation of PI hydrolysis appears to result from activation of the M_1 muscarinic receptor. Moreover, muscarinic stimulation of N-type Ca^{2+} channels is selectively blocked by the effector antagonist function of RGS2 and PI-PLC β1[87].

5.7 Serotonin Serotonin is involved in craniofacial and cardiovascular morphogenesis. Three subtypes of receptor transduce the serotonin-induced mitogenic activity, probably involving PI-PLC. M channels, low-threshold K^+ channels composed of subunits of the KCNQ (Kv7) gene family[88], are inhibited by stimulating $G_{q/11}$-coupled receptors, as for example in sympathetic neurons by M_1-mAChRs and by bradykinin (BK) B_2 receptors[89]. The activated G-protein subunit, mainly $G\alpha_q$, induces closure by an indirect mechanism probably involving PIP2 hydrolysis by means of PI-PLC enzymes[14]. PIP2 is required to maintain KCNQ channels in their open state[90]. Resynthesis of PIP2 is necessary for recovery from the M-channel inhibition produced by mAChRs[91] and by nucleotide receptors[48]. By contrast, BK-induced M-channel inhibition more likely stems from the action of IP3, which closes channels by binding to calmodulin[92]. DAG might contribute to the mAChR-induced inhibition of M channels through activation of PKC and subsequent channel phosphorylation[89]. The PI-PLC δ subfamily is mainly involved in this process[89].

5.8 Metabotropic receptors *L*-glutamate, the major excitatory neurotransmitter in the mammalian central nervous system, elicits physiological effects by activation of both ionotropic and metabotropic (mGlu1–8) receptors[93]. The family of metabotropic glutamate receptors (mGluRs) is divided into three groups, based on pharmacology, sequence homology and receptor coupling. Upon activation, group I (mGlu1 and 5) receptors elevate intracellular Ca^{2+} levels by coupling to G_q/G_{11} proteins, which in turn activate the PI-PLC pathway. Moreover, group I mGluRs are known to elicit epileptiform discharges in the hippocampus through PI-PLC β1 signalling[93]. During development of the cerebral cortex, the invasion of thalamic axons and subsequent differentiation of cortical neurons are tightly coordinated. Glutamate neurotransmission triggers a critical signalling mechanism involving the activation of PI-PLC β1 by mGluRs[94]. Activation of PI-PLC β1 *via* mGluR5 is critical for the coordinated development of the neocortex[45,95]. Prolonged activation of group I mGluRs reduces neuronal susceptibility to excitotoxic injury, as demonstrated by the results obtained after U-73122 treatment of hippocampal cultures[96]. The reduction is associated with a PI-PLC-dependent depression of excitatory synaptic transmission, thus confirming the PI contribution to neurogenesis. N-methyl-*D*-aspartate (NMDA) toxicity might be associated with NO-mediated activation of the PI-PLC δ subfamily[24,97]. Activation of group I mGluRs by (*S*)-3,5-dihydroxyphenylglycine, prior to NMDA exposure, reduces hippocampal susceptibility to NMDA-induced injury[93,94]. The reduced susceptibility is probably associated with PI-PLC-dependent reduction of synaptic excitation. The involvement of PI-PLC suggests that the group I mGluR-mediated reduction of susceptibility to injury may also affect neurogenesis[23,45].

5.9 Growth factors *Drosophila* border cells migrate in two phases using distinct mechanisms. Polarized cell behavior is critical for the initial phase of migration, whereas dynamic collective behavior dominates later. Receptors associated with platelet-derived growth factor, vascular endothelial growth factor, and epidermal growth factor act in both phases, using different effector pathways[24]. Raf, PI-PLC γ or PI3-OH-kinase are not uniquely required for migration; however, the pathways might act redundantly. Simultaneous perturbation of Raf and PI-PLC γ impairs migration. The latter migratory phase in the gene expression pattern is later, posterior and dorsally directed and requires Raf/MAPK or PI-PLC γ involvement[24].

5.10 Thyroid hormones The developmental effects of thyroid hormones in the mammalian brain are mainly mediated by nuclear receptors regulating gene expression. However, nongenomic mechanisms have also been described, associated with kinase- and calcium-activated signaling pathways consistent with the existence of one or more membrane binding sites for the hormones. L-thyroxine (L-T_4) acts upon intermediate filaments, which form the cytoskeletal framework[98]. The mechanisms underlying the L-T_4 effect on the cytoskeleton involve membrane-initiated actions through Gi protein-coupled receptors and require the participation of PI-PLC, PKC, MAPK, and Ca^{2+}/calmodulin-dependent protein kinase II. First, L-T_4 interacts with a GPCR at the cell membrane causing reduced cAMP levels and PKA activity. After hormone-binding, PI-PLC, PKC and MAPK are serially activated[99].

5.11 Calcium-permeable channels The family of Ca^{2+}-permeable channels, TRPCs, formed by homomeric or heteromeric complexes of proteins containing six transmembrane domains, is activated through a PI-PLC-dependent mechanism. TRPC expression begins early in embryonic development and remains in adulthood. In fact, TRPCs play important roles in a number of events required for neuronal development, including proliferation, cerebellar granule cell survival, axon pathfinding, neuronal morphogenesis, and synaptogenesis. TRPCs are thought to act as cellular sensors. Ca^{2+} influx through TRPCs 3 and 6 activates CaMK and MAPK to phosphorylate CREB[4], leading to neuronal survival. CREB is considered to be the point of converence for both activity-dependent and TRPC-induced survival signaling[100].

5.12 Tenascin The extracellular matrix (ECM) glycoprotein tenascin-C (Tnc) both stimulates and inhibits axon outgrowth, depending on the means of presentation or the domain composition[101]. Tnc is transiently expressed by astrocytes and displays a boundary-like distribution in some areas during the development of axonal pathways. Tnc plays an essential role in cortical development and function, in the modulation of hippocampal learning and plasticity, in behavior, and in neurotransmission[101]. Based on its multimodular structure, Tnc interacts with various proteins in the ECM or on the cell membrane. Studies based on recombinant technology and pharmacological analyses highlighted that Ca^{2+}-dependent signaling pathways are of critical importance for the stimulatory effect of Tnc on neurite growth. This seems to be contactin-dependent and involves the activation of PI-PLC, as well as the liberation of Ca^{2+} from intracellular stores[101]. Evidence supports the proposal that, in Tnc-dependent neurite outgrowth, β1-integrins are essential for phosphorylation of PI-PLC γ1, formation of protein complexes, and accumulation of intracellular Ca^{2+}[102]. This suggests the existence of a direct link from Tnc receptors to PI-PLC-mediated Ca^{2+} signalling. Interestingly, direct interaction of Ig superfamily members with integrins has been reported, confirming that neurite outgrowth depends on a Ca^{2+}-dependent pathway. Further studies on IP3 downstream targets such as PKC or calmodulin kinase confirm the involvement of PI-PLC enzymes in Tnc signal transduction[102]. Moreover, contactin is a receptor for a specific Tnc domain (TNfnBD)[103]. The PI-PLC γ1 isoform is probably the linchpin for TNfnBD-dependent signaling. In fact, neurite length decreases after treatment with inhibitors of PI-PLC due to reduced growth cone velocity.

5.13 Brain-derived neurotrophic factor (BDNF) Stimulation of the dopamine D1-D2 receptor heteromer activates a signalling cascade connecting dopamine signalling, BDNF production and neuronal growth through a cascade of events, primarily the mobilization of intracellular Ca^{2+}

via G_q, PI-PLC and IP3[104-106]. Then, a cascade of events follows, such as the rapid activation of cytosolic and nuclear Ca^{2+}/calmodulin-dependent kinase II α and increased BDNF expression, as well as the maturation and differentiation of striatal neurons, marked by increased MAP2[104].

5.14 Papaverine Papaverine, an inhibitor of phosphodiesterase 10A has neuroprotective/neurotrophic actions. Papaverine potentiates NGF-induced neurite outgrowth in PC12 cells in a concentration-dependent manner. The potentiation of NGF-induced neurite outgrowth by papaverine is blocked by U-73122, by simultaneous administration of IP3R antagonists, and by reduced expression of the IP3R gene. PI-PLC γ and IP3R might be involved in the mechanism underlying the effects of papaverine on neurite outgrowth[63].

5.15 Homocysteine (Hcy) Hcy acts upon cytoskeletal phosphorylation during rat hippocampal development and induces neurotoxicity by activating the intermediate filament-associated phosphorylation system through different signaling mechanisms. The involvement of NMDA receptors and voltage-dependent channels has been described during the uptake of Ca^{2+}. Ca^{2+} release requires the participation of PI-PLC, PKC, MAPK, phosphoinositol-3 kinase and Ca^{2+}/calmodulin-dependent protein kinase II[104].

6 Conclusion

The PI signal transduction pathway is involved in the Ca^{2+} signaling cascade during neuronal development, as well as in the maintainance of neural plasticity and in synapse formation. PI-PLC enzymes act in different events, influencing the activity of several molecules, at several levels in the control hierarchy. PI-PLC enzymes are also involved in the inflammatory activation of glia[41]. Recently, the involvement of PI-PLC isoforms in the aetiopathogenesis of rat astrocytoma[42] and in human neuroblastoma has been raised[41].

The PI-PLC family of enzymes also contributes to neural development through a complex interaction network in a time-dependent manner. The functional interconnection between the PI signal transduction system and the network of signaling pathways that regulate neural development deserves attention. In fact, PI-PLC β1 loss-of-function, following homozygous deletion of PLCB1, led to the death of a child with congenital epileptic encephalopathy[49]. This supports the hypothesis that PI-PLC enzymes play critical roles in neural development. Moreover, the possible roles of PI-PLC enzymes in the aetiopathogenesis of nervous system illnesses, such as mental retardation[65] and different affective disorders[41,50,65,107], major depression[65] and schizophrenia[65,107] have been investigated. These observations suggest that PI-PLC enzymes might be involved in the alteration of neurotransmission. However, the nature, the meaning, and the developmental period of PI-PLC action are still largely unclear and require further studies.

Although considerable research efforts have been made to delineate the metabolic pathways in the nervous system, further studies are required to fully elucidate the complex interplay of the signalling molecules, with specific regard to the embryonic period. Besides the increase in our knowledge of the events that regulate neural development, understanding the role and the timing of action of the signaling pathways during neurogenesis will allow clarification of the aetiopathogenesis and the clinical history of several central nervous system diseases. This will be helpful in diagnosis and prognosis, which often are difficult to characterize.

Defining the role of the PI signalling system and its relationships with other signalling pathways in the developing nervous system will improve our knowledge of neural development. Elucidating these questions will help reveal the pathogenesis of diseases of the nervous system, as well as pave the way for identifying novel therapeutic strategies.

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